

On the Opioid Crisis and the Future of Pain Treatment

An Interview with Bertha K. Madras, PhD

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We are currently facing an opioid epidemic in the United States, with deaths related to opioid abuse tripling over the past two decades [1]. The addiction potential of opioids stem from their analgesic and euphoric properties through binding to the brain's opioid receptors [2]. These opioids include illicit substances like heroin, but also prescribed drugs like morphine and oxycodone. Here, I interviewed Dr. Bertha K. Madras who provides a timely introduction to the root causes of the current opioid crisis, and discusses actions necessary to overcome it.

Dr. Madras is a psychobiologist at McLean Hospital and a professor of psychobiology in the Department of Psychiatry at Harvard Medical School. She earned a Doctor of Philosophy degree from McGill University studying tryptophan metabolism and hallucinogen pharmacology and held post-doctoral fellowships in biochemistry at Tufts University and Massachusetts Institute of Technology. During her tenure as a scientist she chaired the Division of Neurochemistry at the New England Primate Research Center, and served as the Deputy Director for Demand Reduction in the Office of National Drug Control Policy (ONDCP†) during the Administration of former President George W. Bush. Currently, she is a member of the President's Commission on Combating

Drug Addiction and the Opioid Crisis (the "opioid commission") and contributed to the Commission's recent report putting forth recommendations to combat the current addiction crisis [3]. Dr. Madras has published more than 190 original research articles, essays, and reviews, holds 19 patents, and continues to pursue her fascination with the neurochemical foundation of addiction and neuropsychiatric disease through her research program.

Dr. Madras, your early career research as a Principal Investigator focused on drug addiction, specifically through the study of cocaine; what did you learn about cocaine addiction, or drug addiction more generally, from your early research?

The most interesting thing we learned about cocaine addiction were cocaine's principal targets in the primate brain, the dopamine transporters. We learned that a series of drugs that bind the dopamine transporters with a rank order of potency correlated with their rank order of potency in promoting self-administration and psychomotor stimulation. By identifying the dopamine transporter as a target, we were able to hone in on a signaling system to target medications for treating cocaine addiction: the

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†Abbreviations: ONDCP, Office of National Drug Control Policy; SPECT, single-photon emission computed tomography; AMA, American Medical Association; CMS, Centers for Medicare and Medicaid Services; CPT, Current Procedural Terminology; SBIRT, Screening, Brief Intervention and Referral to Treatment.

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transporter and dopamine receptor subtypes. Hundreds of novel compounds were designed and tested but alas, it dawned on us that this goal was far more challenging and elusive than we believed during the optimistic early days of discovery. In the meanwhile our drug discovery program led to many other exciting leads which we doggedly pursued. From that study came many different leads and the goals expanded into developing probes for the transporter and applying them to a number of other neuropsychiatric conditions.

The probes that I developed in my lab originally, in 1989, were designed to circumvent the very poor properties of cocaine, including very rapid association/dissociation kinetics. So, I decided to find a substitute for cocaine to target the same sites but with a much better pharmacokinetic profile. I scoured the literature and identified a number of possible drugs that we could either synthesize from scratch or else just radiolabel. Of the candidates, one of them, originally developed by Winthrop Sterling, WIN-35428, turned out to be remarkably selective and potent at the dopamine transporter if radiolabeled with tritium. So selective that I still have the original graphs generated that memorable day March 1, 1989, when a research assistant in my lab, Michele Fahey, came to the office and showed them to me. I took one look at them and said this is going to be a brain imaging agent for the dopamine transporter – that was my comment to her, because the data were so crispy clean and non-selective binding was so low. From that moment on I generated collaborations to develop this compound into a brain imaging agent. Marc Kaufman, a post-doctoral fellow, and I used it to map the dopamine transporter with exquisite clarity in various regions of primate brain. Shortly thereafter, I requested post-mortem brains from Parkinson's disease patients from a brain bank, because I thought the transporter would be a sensitive marker for the disease and would be a very sensitive, diagnostic test for the disease. With autoradiography, we looked at the distribution and binding properties in the human brain, and true to predicted results, the probe turned out to be exquisitely sensitive in detecting Parkinson's disease.

From that moment on my research was no longer in a relatively quiet corner of science because many people jumped on the band wagon wanting to develop similar agents. We forged ahead developing PET (positron emission tomography) and SPECT (single-photon emission computed tomography) imaging agents to detect Parkinson's disease, and imaged Parkinson's diseased patients, and persons with ADHD (Attention-deficit/hyperactivity disorder) reasoning that as ADHD drugs, anti-hyperactivity drugs, target the dopamine transporter, conceivably persons with ADHD may harbor abnormal transport densities. From then on, the research just cascaded into other areas, including genotyping the transporter in ADHD, de-



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veloping candidate medications for Parkinson's disease and branching further into other areas of research. Many people tried to devise their own analogs of WIN-35428 (also known as CFT) to patent and market them, and at least 20 analogs were made worldwide, and applied to over 25 neuropsychiatric conditions. One of our analogs, Altoprane, is being used for a depression study here at McLean by a person who I didn't know. Altoprane is an analog we developed for both PET and SPECT imaging.

Taking a step back, how did you first become interested in the study of drug addiction and neuropsychiatric disease?

I was interested in neuroscience research as an undergraduate. I was 16 years old and in the honors biochemistry program. We were given a choice of writing a paper on a specific topic in biochemistry from a list of 10 topics and were told if you don't like any of these 10 just find your own topic, which was the kind of freedom I enjoy.

I decided to write a paper on phenylketonuria, an inborn error of metabolism that involves the loss of function of the enzyme phenylalanine hydroxylase. As a result, phenylalanine builds up in the blood and the child who is born with this disorder, within a period of time, undergoes brain damage. I was stunned at the fact that if you test for phenylketonuria within a day or so of a child being born, because excess phenylalanine can be found in blood after birth (the mother protects the baby until birth), or phenylketones in urine, and put the afflicted newborn on a low phenylalanine diet to eliminate excess phenylalanine; their IQs can be normal, and they can develop essentially normally. But, if you don't test and don't alter their diets, they can end up brain damaged depending on how severe the genetic anomaly is. This was the most

amazing thing I learned in college. The fact that you can change the course of a child's life in terms of brain function just by doing a simple test and knowing metabolism and these simple amino acids in the brain. And that was it. I was hooked for life and went into neuroscience.

Your training in neuroscience and your research as a Principal Investigator led you then to be selected to work for former President George W. Bush as the Deputy Director for Demand Reduction in the ONDCP. What were the main issues facing the United States at that time with regards to substance abuse, and what would you say was one of your biggest accomplishments while serving the former President?

Well, we faced many problems. People have forgotten that we had a cocaine problem, a prescription drug problem, and a fentanyl outbreak in 2006. Few remember it; nobody even mentions it. This fentanyl was also illicit; it was not a prescription medication giving rise to the deaths. We had a number of cities in the northeast and in the mid-Atlantic states – Detroit, Pittsburgh, Philadelphia, Chicago – where there were over a thousand deaths by 2007. Within a few months of being in office, the clips showed several people were dying on a daily or weekly basis, and I said we have to do something about it. So, I organized a fentanyl conference in Philadelphia, which brought together emergency department physicians, first responders, law enforcement, academics, biologists, and medical examiners into one room, to coordinate a response. It turned out the fentanyl was being produced in a “super lab” in Mexico, and when that “super lab” disappeared, the death rates went back to baseline.

That was an acute problem. The much more important problem in terms of national impact was that the medical community was derelict in a number of ways, primarily because it largely ignored substance use in patients and ignored the prescription opioid problem, which was of growing significance. The first trip I took on assuming office was to the headquarters of the American Medical Association (AMA) to plead for educating physicians on screening for substance use, addiction, and for prescription opioid addiction. If we don't screen patients for substance use and use disorders we are going to end up with a national catastrophe. Prescription opioids are increasingly the cause of deaths and addiction. I proclaimed that you don't prescribe alcohol or tobacco, you prescribe opioids, and it's in your domain to do something about it. If we get billing codes, which sets aside time for physicians to screen which they can bill for, maybe perhaps we can catalyze a movement throughout the country in this neglected area of medicine.

After months, the CMS (Centers for Medicare and Medicaid Services) adopted Medicare codes for Screening, Brief Intervention and Referral to Treatment (SBIRT). But, I knew based on my reading, that unless we get what are called CPT codes (Current Procedural Terminology), which are endorsed by the AMA, use of the Medicare or Medicaid codes would be minimal. I didn't need to pressure. By September I got a letter from the AMA inviting me to their billing code approval annual meeting, and I assembled a team to petition the board to adopt these codes. They denied the petition but after re-submitting again, we got them. From that point on SBIRT was catalyzed throughout the country. So, I hoped it would enable physicians to screen for patients' substance use, and catalyze medical education in this domain.

I organized a medical education conference to try to convince professional associations and medical schools to educate physicians on the importance of screening all patients, as well as learning about opioid prescribing and pain management. Those goals, presented at three conferences were attended by over two hundred people at each. We also published the first Federal SBIRT program outcomes from a population of 459,599. From that point on, the number of manuscripts devoted to screening increased dramatically. Until that point SBIRT festered gathering dust, electronic dust; many hospitals and organizations now require screening for substance use of all their patients.

As of last year, you have been serving the current Administration as 1 of 6 members on President Trump's “opioid commission.” The commission published a report in November of last year; what were the main findings regarding opioid abuse in the United States and what were some of the primary recommendations set forth in the report?

I was asked by Governor Christie who chaired the commission to shepherd the report and to write it. I had tremendous help and input from other Commissioners and from many knowledgeable people. I went on a listening and research literature tour, and by July 7th had 253 topics on my computer for the final report. Governor Christie said, let's simplify it; which we did.

Over-prescribing of prescription opioids gave rise to this crisis. Initially an iatrogenic disease of addiction and death. The number of overdose deaths in 2016 due to opioids was over 40,000, with 20,000 additional other deaths due to a different array of drugs. The introduction of heroin and fentanyl began later as prescribing began to diminish and abuse-deterrent formulations were developed. For example, oxycontin, the extended release formulation, was made into a formulation difficult to crush

and to inject. As a result, the entrepreneurs on the dark side stepped up and began to distribute very inexpensive and very pure heroin. By 2013, we saw the rise once again of fentanyl, and fentanyl has changed the scene dramatically. I felt with prescription opioids this problem can be contained with some complex but very clear solutions, by eliminating or reducing unnecessary prescribing, reducing first time exposure to opioids, and so on. But fentanyl has presented a different challenge, because unlike the 2006 crisis where a single producer in Mexico could be identified and a few minor manufacturers in California, in this case the bulk of the manufacturing is being done in a number of labs in China, and a few in Mexico, but the distribution is very complex. It is being sent in envelopes, manila envelopes, which are much harder to detect, and using the U.S. Postal Service rather than carriers and couriers. So, it is very different than it was, and much harder to deal with; interdiction is clearly one of the solutions. Reducing the supply of prescription opioids, of heroin, of fentanyl, is clearly one of the multipronged solutions.

We learned of major gaps that needed repair and innovative responses. Within the 56 recommendations of the final report, we focused on developing modern methods for prevention, on reducing prescription opioids by expanding medical education, establishing prescription drug monitoring programs, and adhering to CDC (Centers for Disease Control and Prevention) guidelines for opioid prescribing. We acknowledged major gaps in our treatment system, and the need to increase treatment slots, reduce treatment waiting times, improve treatment quality, increase availability of effective medications to treat opioid addiction, reduce insurance burdens, and increase drug courts. In the domain of overdose rescue, we proposed expanding access to the overdose rescue drug naloxone, increasing the numbers of people trained to administer it, and training recovery coaches to assist people who have been rescued transition to treatment. Data analytics was another section of the report for it recognized the power of big data sets and acquiring them in real time. We proposed a number of applications for big data analytics that could facilitate more timely responses to weaknesses in our system. We also focused on providing recovery homes with improved standards and expansion of drug courts in the federal system to address people with substance use disorders within the justice system. Another gap which the recommendations were designed to close is a reporting and accountability gap. We proposed that all federal expenditures be subjected to quantifiable goals and outcome measures, and be tracked. Other important recommendations can be gleaned from the Commission Report.

In terms of prevention, you have named a few options, but I know you also study the effects of cannabinoids on human neurochemistry;

Cannabis is one drug that has been explored as a potential alternative for pain treatment, including in cancer patients as well as for those with multiple sclerosis; what are your thoughts on cannabinoids as a viable option to treat pain?

The recent National Academies of Sciences, Engineering, and Medicine report summarized what over 15 meta-analyses have already concluded. The vast majority of the medical indications for whole plant marijuana embedded in state regulations have no rigorous scientific basis whatsoever. And for the few randomized controlled trials that have been conducted for chronic neuropathic pain, none have been extended beyond a few weeks and the majority of subjects were experienced marijuana users. It's also important to note that a THC (tetrahydrocannabinol):CBD (cannabidiol) mixture failed in Phase III clinical trials for cancer pain. In many ways the recent history of the marijuana movement is recapitulating the history of the opiophilia movement that has led to our current national crisis.

When you look at the root causes of the current opioid crisis there are many – at least 30 contributors. One of the first contributors was poor science, we had no long-term outcomes on the use of opioids for chronic pain. None. Nothing published that went beyond a few months. We had nothing published on safety and efficacy after years and years of opioid administration. We have precisely the same problem with marijuana with regards to long term use for pain management. We have nothing in terms of randomized controlled trials conducted for long periods and a safety-efficacy profile to include quality of life measures after extended use of the various concoctions designated as medical marijuana. Some of the abstracts I have seen of preliminary data show that people are smoking marijuana 3 to 8 times daily which means that for most of the time they are awake, they are cognitively compromised. So, at this point it is very difficult to endorse a psychoactive, addictive, psychotomimetic plant extract as an alternative without good evidence. We should not go down the same path that we did with opioids which was to accept poor-quality science claiming that they were safe for the long term and non-addictive for pain patients. Think of the many factors that fueled the opioid crisis and the compelling parallels with marijuana. During the development of the opioid movement, vast sums of money were spent to promote their unsubstantiated use for many pain conditions, side-by-side comparisons with safer drugs were not performed, doses were not evidence-based, and they were promoted as safe and not addictive without solid evidence for safety and efficacy for chronic medical conditions. Opioid advocates received attention but prudent opponents were ignored or vilified as drug warriors; addiction, diversion and other

adverse consequences were not anticipated or even ignored. Illicit opioid analogs flooded the nation, medical education lagged far behind the crisis, and government regulations failed to protect the public. Quite similar to today's marijuana movement, wouldn't you agree? We are at the same stage with marijuana and we have to be as cautious.

It is, however, critical to explore the 100 or so cannabinoids in the marijuana plant, and synthetic cannabinoids, fatty acid amide hydrolase (FAAH) inhibitors, and others for therapeutic potential. The research has to go on; it is fascinating, it's important, and there are some candidates within the plant that are intriguing for a number of applications including anti-seizure properties. Cannabidiol is a good example. But it is more complicated. For example, THC and CBD have essentially opposing pharmacological effects: THC is addictive, intoxicating, impairs cognition, is a psychotomimetic, can be anxiogenic, and pro-, or anti-convulsant. CBD is not intoxicating, not addictive, not psychotomimetic, can be anxiolytic, anticonvulsant, and possibly even anti-psychotic. Whole plant marijuana has various ratios of the two compounds. Plant breeding has greatly increased the THC:CBD ratio, but without a scientific rationale. Another example, THC targets both CB₁ and CB₂ cannabinoid receptors, and in certain medical conditions the CB₂ receptor is beneficial, or the CB₁ receptor is malevolent, and having a drug that hits both of them when one of the two targets could in fact be counterproductive makes no sense at all. At this point we need to promote high quality, rigorous research and move away from the misinformation flooding the media with reports of miracle cures and non-addictive properties and perfect treatments to manage chronic pain. Even the National Academies report on marijuana had a deep flaw in it drawing the conclusion that evidence exists for the use of marijuana in chronic pain conditions – quality evidence does not exist. It was problematic to report this conclusion, without adequate evidence.

How then do you see the future of pain treatment? Are there any promising alternatives to opioids if not within the components of marijuana?

Pain is a complex issue. There are many different types of pain, different origins of pain, and different perceptions of pain depending on one's affect and mental health status. Depressed people, people who are anxious, who are stressed, who have a greater propensity to have psychiatric problems, conceivably may perceive pain differently than people who do not harbor underlying psychological burdens. So, when we talk about pain management, it is not simple. What type of pain? Neuropathies are different than acute bone pain, or ankle pain, or migraines, or tooth extractions. We have to look

to some prudent countries. Many countries treat as a first pass, ordinary pain with nonsteroidal, anti-inflammatory drugs (NSAID). Data are emerging that show that these drugs, over-the-counter, can be as effective as opioids at treating different types of pain. One of the 30 root causes of the opioid crisis was intense pressure on physicians to use opioids to treat pain in all its forms when the evidence wasn't there, and when alternatives are just as effective and much safer and have no psychoactive properties and don't affect the brain.

Most encouraging is an initiative by the National Institutes of Health (NIH) and its institutions, especially the National Institute on Drug Abuse (NIDA), to embark on a journey of drug discovery with the goal of developing safer effective analgesics: opioids with neither addictive potential nor respiratory depression, or compounds that target other sites in pain pathways either in brain or in the periphery.

Do you have any final comments or thoughts on the origin of substance abuse problems, and/or the treatment of substance abuse disorders?

We have become a nation that has normalized chemical coping and chemical reward without realizing that chemical coping and chemical reward can lead to a modern form of slavery, chemical addiction. We have to begin de-normalizing the use of drugs to artificially reward our brains or to cope with life. We are accustomed to assuming that life should be perfect and stress free and beautiful every day. Life is full of stressors and of challenges which can be resolved and can give rise to pleasant and serene periods, and then decline into periods of stress. Americans are so universally optimistic and hopeful that the downside to our optimism and hope is a desire to maintain perfection daily; let's pop a chemical to cope with life or pop a chemical to yield an instant easy reward. The consumption of drugs, which in the words of Arthur Koestler, play confidence tricks on one's mind, achieves neither serenity nor perfection over time.

If you look at the history of the opioid crisis all the regulations that we had in place for Schedule II and Schedule III drugs, manufacturing quotas, chain of custody, prescriptions, tight regulations, did not protect the American public in the face of massive publicity, massive disinformation, massive campaigns to market opioids, and pressure on physicians to prescribe them. I fear that we are currently in the same situation with marijuana.

Finally, we can't *arrest* our way out of the opioid crisis, we can't *treat* our way out of the opioid crisis, and we can't *prevent* our way out of the opioid crisis. We have to do all three.

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